

Underactive bladder: A review of the current treatment concepts

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Cite this article as: Bayrak Ö, Dmochowski RR. Underactive bladder: A review of the current treatment concepts. Turk J Urol 2019; 45(6): 401-9.

ABSTRACT

According to the International Continence Society standardization reports, underactive bladder (UAB) is a decrease in detrusor contraction and/or shortening of the contraction time, resulting in an incomplete and/or prolongation of the bladder emptying within the normal time frame. It has been indicated that idiopathic, neurogenic, myogenic, and iatrogenic factors play a role in the etiology. To make a diagnosis, it is absolutely necessary to perform a pressure-flow study. Treatment alternatives are generally based on the evacuation of the lower urinary tract, independent of the etiology. UAB treatments are listed under the headings of conservative methods and clean intermittent catheterization, pharmacotherapy (alpha-blockers, cholinesterase inhibitors, muscarinic agonists, prostaglandin E2, and acotiamide), surgical treatments (sacral nerve stimulation–electrical stimulation, injections into the external sphincter, surgeries to be performed for bladder outlet obstruction, reduction cystoplasty, and latissimus dorsi detrusor myoplasty), and stem cell and gene therapies. It is still controversial whether satisfactory success is achieved in the treatment of patients with UAB. Owing to the better understanding of the pathophysiology, future developments in the pharmaceutical industry, gene therapy, and biomedical applications are expected to close the gap in the treatment.

Keywords: Clean intermittent catheterization; pharmacotherapy; surgical treatments; underactive bladder.

Introduction

According to the 2010 International Continence Society standardization reports, underactive bladder (UAB) is a decrease in detrusor contraction and/or shortening of the contraction time, resulting in an incomplete and/or prolongation of the bladder emptying within the normal time frame.^[1] In their study, Resnick et al.^[2] described UAB as the inability to empty the bladder in men and women without an increase in intra-abdominal pressure. In 1996, they defined UAB as failure to induce emptying of at least half of the bladder with involuntary recurrent contractions without the evidence of straining, urethral obstruction, and detrusor sphincter dyssynergia.^[3] However, Valentini et al.^[4] described UAB in women as prolonged voiding time and impaired detrusor contractions, leading to increased post-void residual urine (PVR). As seen in previous studies, in patients with UAB, symptoms related to incomplete bladder emptying dysfunction, such as decrease in maximum flow rate (Qmax), increase in PVR volume, and prolonged urination time, are frequently reported.

According to the results of pressure-flow studies in patients with non-neurogenic lower urinary tract symptoms (LUTS), UAB has been detected in 9%–28% of males under the age of 50 years old and 48% of those over 70 years old. In older female patients, the prevalence varies between 12% and 45%, and it can be observed in patients with impaired contractility due to detrusor hyperreflexia.^[5,6]

Etiology

Idiopathic (unknown cause in young patients and normal aging process), neurogenic (Parkinson disease, diabetes, multiple sclerosis, Guillain-Barre syndrome, spinal-lumbar disc hernia, spinal cord injury, spinal stenosis, and spinal dysraphism), myogenic [bladder outlet obstruction (BOO) and diabetes], infectious (neurosyphilis, herpes zoster, herpes simplex, and acquired immunodeficiency syndrome), and iatrogenic (pelvic surgery, radical prostatectomy, radical hysterectomy, anterior resection, and abdominoperineal resection) factors play a role in the etiology of UAB.^[1,6] Among these factors, neurological disorders,

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Submitted:
07.12.2018

Accepted:
11.12.2018

Available Online Date:
04.02.2019

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Available online at
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age-related factors, BOO, and diabetes have been emphasized as the major etiological factors causing UAB (Table 1).^[6,7]

In recent studies, the role of the urothelium in patients with urodynamic UAB has been investigated. In the study by Cho et al.,^[8] the bladder mucosa of 15 male patients diagnosed with UAB was biopsied. Adenosine triphosphate (ATP) levels were shown to be lower in patients with normal detrusor contraction. In addition, a significant correlation between ATP with bladder contractility index (BCI) and detrusor pressure at maximum flow (Pdet@Qmax) was reported. In the study by Jiang and Kuo,^[9] patients with UAB were evaluated for urothelial signal functions. Decreases in E-cadherin, muscarinic receptor 2/muscarinic receptor 3 expressions, and levels of endothelial nitric oxide synthase and increases in beta-3 adrenoceptor expression, apoptotic cells, mast cells, and purinergic receptors were indicated in bladder biopsy specimens of patients with UAB.

Diagnosis

To make a diagnosis, it is necessary to perform a pressure-flow study. Decrease in Qmax related to BOO or poor contractility can be distinguished by pressure-flow study. To assess the contractility of the bladder, BCI as defined by Abrams is frequently used. BCI is calculated from the Qmax and Pdet@Qmax according to the equation $Pdet@Qmax + 5Qmax$. Accordingly, BCI is considered to be strong (BCI>150), normal (BCI 100–150), and weak (BCI<100).^[10] In addition to this formulation, similar diagnostic criteria have been reported in different studies, and the following formulations have been proposed:

- Fusco et al.^[11]: Pdet@Qmax ≤30 cm H₂O and Qmax ≤12 mL/s (in men),
- Abarbanel and Marcus^[12]: Pdet@Qmax<30 cm H₂O and Qmax<10 mL/s (in men and women),
- Jeong et al.^[13]: BCI<100 (in men), Qmax ≤12 mL/s, and Pdet@Qmax ≤10 cm H₂O (in women).

Treatment of UAB

There is no definitive protocol for UAB treatment that will significantly improve the quality of life (QoL) of patients and will significantly contribute to the prevention of complications. Treatment alternatives are generally based on an empty bladder, independent from the etiology. The priority target is to increase the contribution and compliance of patients to the treatment process; this prevents possible damage to the upper urinary tract. At this stage, the risk of recurrent urinary tract infections (UTIs), bladder stone formation, overflow incontinence, urinary retention, impaired renal function, and chronic valsalva voiding should not be underestimated. The side effects of the planned treatment should be easily tolerated by patients. UAB treatments include mainly conservative methods and clean intermittent catheterization (CIC), pharmacotherapy, surgical treatment, and stem cell and gene therapies (Table 2).^[7,14]

Conservative Methods and CIC

Since bladder dysfunction does not show any signs in the early stages, treatment recommendations should be made even if the patients are asymptomatic. Especially in patients with diabetes, because of the loss of sensation in the bladder and an increase in bladder capacity, the progression of the disease is not noticed, and most of the patients are diagnosed late with regard to urological evaluation. Therefore, patients should be called for frequent follow-ups, including urodynamic examination in case of need. If symptoms, such as voiding symptoms and increased amount of PVR, are detected, they should be included in the treatment program. Since this group of patients tend to delay urination, timed, double, or triple voiding may be recommended.^[15] The amount of PVR can be reduced using the Crede or Valsalva maneuver. However, these maneuvers are contraindicated in patients with vesicoureteral reflux, increased intravesical pressure, and vagal reflex. Patients should be instructed not to become constipated, and

Table 1. Etiology of the underactive bladder (adapted from reference 6)

Idiopathic	Neurogenic	Myogenic	Iatrogenic	Infectious
Aging*	Parkinson disease	BOO*	Pelvic surgery	Neurosyphilis
Unknown cause in younger patients*	Multisystem atrophy	Diabetes*	- Radical prostatectomy	Herpes zoster
	Diabetes*		- Radical hysterectomy	Herpes simplex
	Multiple sclerosis		- Anterior resection	AIDS
	Cerebral stroke		- Abdominoperineal resection	
	Guillain-Barre syndrome			
	Spinal-lumbar disc hernia			
	Spinal cord injury			
	Spinal stenosis			
	Spinal dysraphism			

*Main etiological factors. BOO: bladder outlet obstruction; AIDS: acquired immunodeficiency syndrome

Table 2. Treatment of underactive bladder and promising alternatives**Conservative methods and clean intermittent catheterization****Pharmacotherapy**

Alpha-blockers
 Cholinesterase inhibitors (distigmine, pyridostigmine, neostigmine)
 Muscarinic agonists (bethanechol and carbachol)
 Prostaglandin E2
 Acotiamide

Surgical methods

Sacral nerve stimulation–electrical stimulation
 Other surgical methods
 Injections into the external sphincter
 Surgeries for bladder outlet obstruction
 Reduction cystoplasty
 Latissimus dorsi detrusor myoplasty

Stem cell and gene therapies

relevant recommendations on diet and medical treatment should be provided. Avoidance of food that may cause urinary retention should be suggested.^[14]

In spite of these measures, CIC should be recommended for patients with significant PVR and urinary retention. Informing the patient and his/her family about the advantages of this practice is important for patient compliance. A significant number of patients have difficulty in continuing catheterization at later times. Generally, 12–16 French catheters are used, and the daily average number of CIC is determined to be between 4 and 6 times. Ideally, the amount of urine should not exceed 400–500 cc at every application of CIC. Silicone catheters should be preferred because of the risk of encrustation and higher risk of latex allergy especially encountered in the neurourological patient population. The European Association of Urology (EAU) guidelines indicate that CIC is the standard of care in the management of the patient group who cannot effectively empty their bladders. In this group of patients, it is emphasized that transurethral catheterization and suprapubic cystostomy should be avoided due to complications, such as an increased risk of UTI, encrustation, leakage, discomfort, urethral erosion, and bladder spasm.^[16] It should not be disregarded that both CIC and indwelling catheters will reduce the QoL of patients and cause emotional stress. In addition, CIC has particular challenges for certain groups of patients, especially in the elderly, visually impaired, mentally handicapped, and those with limited manual dexterity. It is considerable to state that CIC is not without complications, including urethral

strictures, urethral false passages, hematuria, bacteriuria, and labial erosion.^[17]

The inFlow™ Intraurethral Valve-Pump and Activator (collectively called inFlow) device was approved by the Food and Drug Administration (FDA) since 2014. inFlow assists urine drainage in patients who have urinary retention due to UAB. It is inserted into the urethra and replaced for 29 days. It is a short self-retaining silicone catheter including an internal valve and pump mechanism that uses a miniature magnetically coupled pump activated by a hand-held remote control. When the patient activates the remote control by holding it over her pelvis and pushing the button, urine is actively pumped from the bladder to mimic normal voiding. When the button is released at the end of micturition, a valve is engaged within the device that stops further flow of urine.^[18] In a multicenter study of intraurethral valve-pump catheter in women with a hypocontractile or acontractile bladder, Chen et al.^[19] compared inFlow versus CIC. A total of 273 women performing CIC were included in the study in 18 centers. The mean age of the women was 48.9 years. Of the 273 women, 169 were withdrawn early from the trial due to initial sitting discomfort and leakage. A total of 77 patients completed the inFlow treatment phase. PVR was comparable during the baseline CIC phase and inFlow treatment phase (20.3 ml vs. 16.1 mL). This study showed that inFlow was significantly superior to CIC in its effect on the QoL. Importantly, UTI rates for inFlow started off slightly lower than those for CIC and reduced with continued usage. inFlow has already been in use in Europe for >20 years. However, it is not currently reimbursed by the “Centers for Medicare & Medicaid Services” or its contractors in the United States. It is possible that the decreased UTI rate related to the ability of the inFlow to mimic normal micturition acts by providing periodic, powerful, and total emptying of urine. Additionally, inFlow is a sterile device that is placed only once per month, whereas CIC requires 4–6 times daily, each of which increases the risk of bacterial infection.

Pharmacotherapy

None of the oral medications used in the UAB is completely effective. The main principle of drug treatment is to increase intravesical pressure and detrusor contractility while decreasing bladder outlet resistance. These agents may be listed as alpha-blockers, which reduce urethral outlet pressure, muscarinic agonists (bethanechol and carbachol) or cholinesterase inhibitors (distigmine, pyridostigmine, and neostigmine), prostaglandin E2 (PGE2), and acotiamide, which ensure bladder contraction.^[20,21]

Alpha-blockers

Patients with chronic BOO have a risk of development of UAB. This is particularly evident especially in older patients

with enlarged prostates. Alpha-blockers decrease BOO-related symptoms and facilitate bladder emptying in patients with neurogenic lower urinary tract dysfunction and benign prostatic hyperplasia.^[20] At the same time, the effectiveness of alpha-blockers has been demonstrated in female patients with voiding difficulty and subnormal maximal voiding velocities. In a trial by Chang et al.^[22], after treatment with 0.2 mg tamsulosin for 6 weeks, 35.1% of the patients had decreased voiding symptom scores by >50%, and Qmax increased by >30%.

In addition, previous studies have shown that the combination of a cholinergic agent and an alpha-blocker is more effective than using each agent separately. In the study by Yamanishi et al.^[23], patients were divided into three groups. Patients in group 1 were treated with cholinomimetic drugs consisting of bethanechol chloride (60 mg/day) or distigmine bromide (15 mg/day), and patients in group 2 received urapidil (60 mg/day) as alpha-blocker. Patients in group 3 underwent cholinomimetics+alpha-blocker pharmacotherapy. After 4 weeks, there was a significant decrease in the International Prostate Symptom Score (IPSS) and PVR volume in the alpha-blocker and combination groups, whereas no change was observed in the cholinomimetics group. Mean and maximum urinary flow rates significantly increased only in the combination group.

In the EAU guidelines, it was emphasized that alpha-blockers (tamsulosin, silodosin, and naftopidil) are effective agents in the patient group with bladder outflow resistance who had PVR and autonomic dysreflexia.^[16] Therefore, in patients with chronic retention and UAB, alpha-blockers should be considered for the initial stage.

Cholinesterase inhibitors (distigmine, pyridostigmine, and neostigmine)

Distigmine is a cholinesterase inhibitor used in UAB. The effects and side effects of distigmine occur with binding to muscarinic receptors and inducing downregulation.^[24] In the study by Sugaya et al.^[25], 18 male and 21 female patients (mean age: 75 years) who used alpha-blockers for at least 4 weeks additionally underwent distigmine pharmacotherapy (5 mg/day) for 8 weeks. IPSS scores, QoL scores, PVR volume, and blood pressures were recorded before and after the administration of distigmine. After 4 and 8 weeks, significant decreases were observed in the IPSS scores, QoL scores, and PVR volumes of patients. Any changes in blood pressure and pulse rate were not observed, whereas a slightly statistically significant decrease was found in serum creatinine levels. Frequent defecation, fecal incontinence, diarrhea, frequent urination, and decrease in physical condition were detected in four patients as side effects.

In conclusion, it was reported that the daily combination of alpha-blocker and 5 mg distigmine could be administered effectively and reliably.

Muscarinic agonists (bethanechol and carbachol)

Bethanechol, another agent used in the treatment, acts similar to acetylcholine and stimulates muscarinic receptors, thereby increasing detrusor tone and contractility of the bladder. It is recommended that it should be taken on an empty stomach three or four times per day. It starts to show its effect after approximately 1 h. Although the expected contraction is realized in the first stage, physiological compliance was not observed to be successful. These agents have side effects, such as nausea, vomiting, diarrhea, gastrointestinal system cramps, sweating, bronchospasm, and visual disturbances.^[14] Owing to their potential side effects, clinicians avoid dose increase in this group of drugs. The most important factors that play a role in the non-response to these drugs include the administration of low doses and the complete myogenic damage in the detrusor.^[20]

Riedl et al.^[26] reported the contribution of electromotive intravesical bethanechol administration for the treatment of acontractile bladder. A 20 mg bethanechol in 0.3% NaCl was administered by electromotive technique. A mean 34 cm H₂O pressure increase was observed in 24 out of 26 patients with neurogenic detrusor areflexia. In 3 out of 11 patients with chronic bladder dilatation, only a 3 cm H₂O pressure increase was detected. In 11 patients who responded positively to electromotive therapy, spontaneous voiding was achieved in 9 patients by oral administration of 25 mg bethanechol. An increase in vesical pressure was not observed in 4 patients who received electromotive treatment, and these patients did not also respond to oral intake of 25 mg bethanechol. In conclusion, it was reported that patients with residual detrusor muscle functions could be found among patients who had atonic bladder and received electromotive administration of intravesical bethanechol. With regard to this important comment, patients who respond to electromotive administration of intravesical bethanechol may benefit from oral or intravesical electromotive bethanechol treatment, and those who do not respond are candidates for CIC. In other studies, cholinergic agonists, such as bethanechol or urecholine, have also been used in diabetic cystopathy, but contradictory results have been obtained.^[27]

Currently, drugs increasing cholinergic activity continue to be used very rarely in clinical practice. Gaitonde et al.^[28] evaluated patients aged ≥18 years old, with the International Classification of Diseases, Ninth Revision, Clinical Modification code including LUTS, neurogenic bladder, and urinary retention, in the

National Ambulatory Medical Care Survey database. A total of 132,281 (0.8%) out of 17,321,630 patients reported that bethanechol was prescribed at their visits. The mean age of the patients was 62.3 ± 2.1 years, and patients had bladder atony (35%), urinary retention (20%), neurogenic bladder (18%), urinary incontinence (16%), and incomplete bladder emptying (10%). The EAU guidelines have emphasized that these drugs with parasympathomimetic effects should not be prescribed for UAB.^[20]

Prostaglandin E2

Prokinetic studies in gastroenterology suggest that PGE2, which is used in cardiology to increase the inotropic activity in smooth muscles, increases detrusor contractions and causes urethral relaxation. PGE2 prevents the release of noradrenaline from sympathetic nerve endings. It is administered intravesically, and a significant increase in intravesical pressure leads to a decrease in maximal urethral closure pressure.^[29,30] Previous studies reported that the effectiveness of PGE2 is limited. It should not be recommended for routine treatment and may contribute to the treatment of patients with UAB who use CIC or permanent catheterization.^[20]

Hindley et al.^[31] investigated the efficacy of oral bethanechol and intravesical PGE2 combination in the treatment of UAB. Nine patients in the treatment group who were treated with bethanechol (4×50 mg/day) and intravesical instillation of PGE2 (1.5 mg in 20 ml of 0.9% saline/week) for 6 weeks were compared with 10 patients who received placebo. In the treatment group, the PVR volume decreased from 426 (405–480) mL to 325 (290–352 mL) ($p < 0.015$), and in the placebo group, it decreased from 576 (539–777) mL to 538 (350–775) mL ($p = 0.09$). In addition, a significant decrease in the number of CICs was observed in the treatment group. The authors stated that PGE2 is an alternative agent that could be used in the appropriate patient group.

Acotiamide

Acotiamide is an oral agent that regulates the motility of the upper gastrointestinal tract in patients with abdominal symptoms related to hypomotility and delayed gastric emptying. It also increases the release of acetylcholine and parasympathomimetic activity by inhibiting acetylcholine esterase activity.^[20] In a trial by Sugimoto et al.^[32], oral acotiamide was prescribed to 19 patients who had been under treatment with distigmine bromide for UAB. After 2 weeks, daily drug dosage was adjusted to 100 mg three times daily, and it was observed that the drug was well tolerated with few side effects. A significant reduction in mean PVR volume from 161.4 ± 90.0 mL to 116.3 ± 63.1 mL was reported ($p = 0.006$). In conclusion, the authors emphasized that acotiamide might be prescribed alternatively in patients who did not respond sufficiently to distigmine.

Surgical Methods

Sacral nerve stimulation–electrical stimulation

Previous studies have shown that sacral nerve stimulation (SNS) and intravesical electrical stimulation are useful in selected patients. Urinary retention and voiding functions occur at different times and with different mechanisms. Structures that stimulate both mechanisms are placed at S2–S4 levels.^[33] For micturition, perineal afferent stimuli must activate parasympathetic neurons reaching the bladder and also inhibit urethral sympathetic and sphincteric somatic reflexes.^[33,34] Pathological mechanisms, such as excessive inhibition of the voiding reflex, pelvic floor spasticity, and/or the loss of voluntary control of pelvic floor muscles, are responsible for urinary retention, which is not related to obstruction. SNS can allow the patients to perceive the pelvic floor and voluntary control of pelvic floor muscles with reducing aberrant neural activity.^[33,35] As a result of multicenter studies, SNS treatment in non-obstructive urinary retention was approved by the American FDA in 1999, and it is currently applied in experienced centers as an effective and reliable method.^[16,36]

In a meta-analysis evaluating the efficacy of SNS in women with non-obstructive urinary retention (Fowler's syndrome), a 299 mL increase in voided volume and a 236 mL decrease in PVR volume were reported. A 54% response rate was obtained in the trial phase, and 70%–80% of the patients who received the response in the trial phase were reported to have successful results.^[37] In the study by Lombardi et al.^[38], the efficacy of SNS in the treatment of pelvic floor dysfunction was evaluated in patients with incomplete spinal cord injury. After a median follow-up of 61 months of 13 patients with urinary retention, it was observed that all patients had an improvement of >50% compared with the baseline, and 38% of the patients discontinued CIC. In a prospective, randomized, multicenter study by van Kerrebroeck et al.^[36], the results of 31 patients who underwent SNS for urinary retention were investigated. At the end of a 5-year follow-up, the mean daily CIC frequency decreased from 5.3 ± 2.8 to 1.9 ± 2.8 , and a success rate of 58% was achieved. The mean volume of catheterized urine during CIC was decreased from 379.9 ± 183.8 mL to 109.2 ± 184.3 mL, and a success rate of 71% was reported.

Transcutaneous or intravesical electrical stimulation was tried in patients with voiding dysfunction who had neurogenic pathology, but was not introduced into routine practice in patients with UAB.^[39] Primus et al.^[40] reported successful results in patients with hypocontractile and acontractile bladders after transurethral intravesical electrical stimulation. Improvement of detrusor contractions was achieved in 39% of the patients, whereas bladder sensation was regained in 75% of the patients. In addition, the need for CIC was relieved in 54% of the patients. When

previous studies with electrical stimulation are evaluated, it is reported that short-term success is observed that decreases with time.^[20,40]

Other surgical methods

Injections into the external sphincter: Although onabotulinumtoxinA injections into the detrusor muscle have been approved by the FDA, there is insufficient evidence to support onabotulinumtoxinA injections into the external urinary sphincter. Despite many studies, there is no standard dosage, and onabotulinumtoxinA injection into the external urinary sphincter is as an off-label regimen.^[41] The reduction of urethral resistance allows easier voiding in patients with UAB by the aid of abdominal pressure. However, the injection of onabotulinumtoxinA into the external sphincter for voiding dysfunction does not demonstrate its effect only by decreasing urethral resistance. It also modulates detrusor contractility by eliminating the inhibitory effects of urethral afferent nerves on the detrusor nucleus. An open bladder neck is a very important factor that helps to overcome urethral resistance with abdominal pressure. Injection of onabotulinumtoxinA into the external sphincter is not helpful if the bladder neck is not opened by the action of abdominal pressure in a patient with UAB.^[42]

In the study by Kuo^[43], 50 IU onabotulinumtoxinA injection was performed through the intraurethral route to patients with UAB due to cauda equina, dysfunctional voiding, peripheral neuropathy, and idiopathic etiologies. After 2 weeks of injections, the patients' median voiding pressure and maximal urethral closure pressure decreased from 56.5 ± 41.2 cm H₂O to 39.0 ± 38.4 cm H₂O and from 65.5 ± 38.1 cm H₂O to 50 ± 32.1 cm H₂O, respectively. In addition, PVR volume decreased from 300 ± 189.1 mL to 50 ± 153.6 mL, and the efficacy of onabotulinumtoxinA injection was maintained for 3 months.

Surgeries for BOO: UAB may accompany LUTS of male patients in 11%–40% of the cases.^[13,44] Chronic BOO can lead to UAB; therefore, surgical intervention may be considered in these patients. Transurethral resection of the prostate, laser prostatectomy, transurethral incision of the bladder neck, and onabotulinumtoxinA injection to the prostate may be performed in patients with BOO and accompanying UAB.^[20] However, the success and efficacy of surgery in patients with UAB are controversial. In a recent review and meta-analysis by Kim et al.^[45], the effect of UAB on transurethral surgery results was examined. UAB was diagnosed with urodynamics preoperatively. The authors emphasized that the improvement in IPSS and Qmax were lower in patients who had preoperative UAB. It has also been reported that the detection of preoperative urodynamic UAB is highly valuable for the exclusion of patients who are not eligible for surgery. Therefore, patients

who had UAB diagnosis preoperatively should be warned that postoperative recovery may be limited, or they may not benefit from surgery.

Reduction cystoplasty: Chronic urinary retention secondary to BOO and/or UAB often results in increased bladder capacity, leading to myogenic decompensation. In patients with UAB without BOO, decreasing the capacity of the bladder with increased volume has led to the idea that it may facilitate bladder emptying. Reduction cystoplasty, which is the most critical point in this method, does not increase bladder contractility, whereas it reduces bladder compliance and may also risk the upper urinary system. Therefore, the place of reduction cystoplasty is very limited and should be performed only in well-selected cases and in patients with residual detrusor contractility.^[20]

Latissimus dorsi detrusor myoplasty: Latissimus dorsi (LD) muscle is a large and flat muscle that is innervated by the thoracodorsal nerve. In LD detrusor myoplasty, the free LD muscle flap is wrapped around the bladder, and neurovascular anastomosis was performed between the lower motor branches of the intercostal nerves and deep inferior epigastric vessels. This is a multidisciplinary approach that will be performed jointly by an expert urologist and a plastic surgeon. As shown in a small series of previous studies, it is a promising treatment in motivated young patients who do not want to undergo CIC.^[17] In the first multicentric study about LD detrusor myoplasty, 24 (8 female and 16 male) patients (median age: 39 years) administering CIC for submotor neuron lesions were evaluated in four centers. The median CIC history before the procedures of the patients was 55 (17–195) months. After a median follow-up of 46 months, 17 (71%) out of 24 patients had spontaneous voiding with an average of 25 mL PVR. The mean BCI increased from 20.1 ± 7.6 to 176.2 ± 25.4 ($p < 0.001$). In 3 patients, the CIC frequency decreased 2–4 times with a mean PVR of 200 mL. In conclusion, the authors emphasized that LD detrusor myoplasty is an effective treatment in a selected group of patients who had acontractile neurogenic bladder.^[46]

Stem Cell and Gene Therapies

Although stem cell therapies are not new treatment modalities, in recent studies, they are emerging as promising alternatives in the management of urological pathologies. The regeneration capabilities of the bladder and urethral smooth muscle cells are limited. Research is particularly focused on the use of multipotent stem cells in the tissue repair stage. The stem cells used for this purpose are generally obtained from skeletal muscles. The use of the skeletal muscle is due to the presence of satellite cells that help tissue repair in case of cell damage in the skeletal muscle cells as opposed to the smooth muscle cells.^[47]

Huard et al.^[48] injected these musculoskeletal cells into the bladder walls of immunocompromized adult mice. On days 5, 35, and 70, the cells containing myosin heavy chain and beta-galactosidase-expressing cells were identified. Tamaki^[49] examined the transformation of these cells into multipotent stem cells and even their differentiation into Schwann cells. In this way, they showed the possibility of regeneration in long-term peripheral nerve damage. Similarly, in previous studies, it has been reported that the synthesis of other proteins, such as factor IX and growth hormone, is also possible.^[50,51] Gene therapy is another method that is expected to be more involved in the treatment options in the upcoming period. Previous studies on this subject are mainly performed through nerve growth factor (NGF). This factor is obtained by coding the herpes simplex virus (HSV) to produce recombinant human NGF (rhNGF). Sasaki et al.^[52] found a significant increase in NGF levels in the bladder and L6 dorsal root ganglia approximately 4 weeks after the injection of HSV-rhNGF into the rat bladder. In addition to NGF, there are other factors obtained by genetic manipulations. In particular, glial cell-derived neurotrophic factor and neurotrophin-3 derived from glial cells have been the subject of previous studies and have been shown to significantly improve neuronal damage in animals with diabetes.^[53,54]

In conclusion, many diseases, predominantly diabetes, can cause the loss of sensation in the bladder and UAB. There are still many unknown factors about UAB. The process is developing quite insidiously and appears to be more common than is thought. It can be said that the treatment of UAB is still not satisfactory, and pharmacotherapy is insufficient. Currently, CIC is the standard treatment in the management of patients who cannot have effective bladder emptying. Previous studies have shown that cholinergic agents contribute to detrusor contraction and facilitate bladder emptying, but it is not recommended to use in practice because of frequent and possible serious side effects. Alpha-blockers (tamsulosin, silodosin, and naftopidil) are indicated as effective agents in the patient group with BOO accompanied with PVR and autonomic dysreflexia. Among the surgical methods, SNS treatment has been approved by the American FDA in the management of non-obstructive urinary retention, and it is currently performed in experienced centers as an effective and reliable method. Owing to the better understanding of the pathophysiology, future developments in the pharmaceutical industry, gene therapy, and biomedical applications are expected to close the gap in the treatment.

Peer-review: This manuscript was prepared by the invitation of the Editorial Board and its scientific evaluation was carried out by the Editorial Board.

Author Contributions: Concept – R.R.D.; Design – Ö.B.; Supervision – R.R.D., Ö.B.; Data Collection and/or Processing – R.R.D., Ö.B.;

Analysis and/or Interpretation – Ö.B.; Literature Search – Ö.B.; Writing Manuscript – Ö.B.; Critical Review – R.R.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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